

Hypertrophic Cardiomyopathy

Diastolic Coronary Vascular Reserve: A New Index to Detect Changes in the Coronary Microcirculation in Hypertrophic Cardiomyopathy

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OBJECTIVES	The present study introduces a modification of the diastolic coronary conductance concept that maintains its sensitive properties to detect changes in the coronary microcirculation in human hypertrophy.
BACKGROUND	Decrements of coronary flow in hypertrophy have been explained by changes in the coronary microcirculation. No measure is available to detect these changes.
METHODS	Doppler velocity catheters were introduced into the left anterior descending artery (LAD) and left circumflex coronary artery (LCx) of patients with obstructive hypertrophic cardiomyopathy (HCM) (n = 11) and into the LAD of cardiac transplant recipients (n = 9). The diastolic coronary conductance was measured at rest and after maximal hyperemia induced by a bolus injection of adenosine. Diastolic coronary vasodilator reserve (DCVR) was calculated as the hyperemic diastolic coronary conductance, divided by the coronary conductance during resting conditions.
RESULTS	Left ventricular outflow tract gradient in the HCM group (83 ± 31 mm Hg) was significantly higher ($p < 0.05$). Septal wall thickness was significantly increased ($p < 0.05$), while wall thickness was unchanged in the posterior wall of the HCM group. The coronary flow reserve was significantly decreased in the HCM-LCx region (to $64 \pm 7\%$ of control) and in the HCM-LAD regions (to $57 \pm 7\%$ of control). The DCVR was only decreased in the HCM-LAD (to $46 \pm 3\%$ of control) and not in the HCM-LCx group ($86 \pm 6\%$, $p > 0.05$). Esmolol did affect the pressure gradient and systolic shortening, but did not affect the maximal diastolic conductance.
CONCLUSIONS	The DCVR, in contrast with the coronary flow reserve, is decreased in those regions that display a disturbance in the microcirculation and may, therefore, offer a new way to study coronary adaptations in patients with hypertrophy. (J Am Coll Cardiol 2004;43:670-7) © 2004 by the American College of Cardiology Foundation

Coronary flow reserve (CFR) has been widely used as an index to evaluate functional disturbances in the coronary circulation (1-5). However, decrements of CFR have also been reported in response to changes in blood pressure and heart rate, parameters that are not directly related to coronary vascular disease (1,3,5,6). To overcome these confounding factors, Mancini et al. (7-10) proposed an alternative approach based on pressure-flow loops. They showed that the coronary conductance during hyperemia was less dependent on changes in end-diastolic pressure, heart rate, and aortic pressure as the "classical" CFR. As a consequence, their approach detected epicardial stenosis very sensitively in animals (7-9) and in patients (11,12).

Coronary flow reserve is also decreased in different forms of hypertrophy (2,3). As hypertrophy is often accompanied by changes in end-diastolic and aortic pressure, application of the maximal coronary conductance concept may also be

appropriate in hypertrophy. However, studies with experimentally induced hypertrophy have indicated that the maximal coronary conductance remains unaffected (13-15) making the original approach less suitable for application in hypertrophy. In contrast, hypertrophy has been associated with an increased resting coronary blood flow, and an index based upon the ratio of baseline over hyperemic coronary conductance might be a more appropriate index to detect disturbances in the coronary microcirculation in hypertrophy. The first aim of the present study is to test this index in humans with varying degrees of hypertrophic cardiomyopathy (HCM).

The underlying mechanisms of the reduced CFR in hypertrophy have been ascribed to changes of the coronary microcirculation (13-18). Classical CFR is based upon velocity averaged over the cardiac cycle and, therefore, incorporates both systolic and diastolic information. Moreover, as systolic wall stress, left ventricular (LV) mass and contractility are changed in HCM; changes in this parameter are difficult to interpret. The conductance used in this study is determined in diastole and might, therefore, be minimally affected by the disturbed extravascular compres-

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Abbreviations and Acronyms

AUC	= area under the curve
CFR	= coronary flow reserve
DCVR	= diastolic coronary vascular conductance reserve
HCM	= hypertrophic cardiomyopathy
HTX	= cardiac transplant recipients
LAD	= left anterior descending coronary artery
LCx	= left circumflex coronary artery
LV	= left ventricular
QCA	= quantitative coronary angiography
ROC	= receiving operator curve

sion. To evaluate this line of reasoning, we tested: 1) whether the ratio of cardiovascular conductances depends on the degree of (preceding) systolic compression, and 2) whether this index is able to detect changes in the coronary microcirculation.

METHODS

Patient population. Studies were performed in two different populations: patients with HCM (n = 11), who were referred for cardiac catheterization, and a control group consisting of asymptomatic cardiac transplant recipients (HTX) (n = 9) undergoing routine follow-up coronary angiography one to five years after transplantation. Informed consent was obtained in all patients. Patients in the HCM group were symptomatic, New York Heart Association class II or III, despite beta-blockade therapy and/or therapy with calcium-antagonists. Six of 11 HCM patients smoked, one was hypertensive, and none of them were diabetic. In all HCM patients, myectomy-myotomy was performed, and the tissue was collected for histological analysis. Left ventricular biopsies were obtained from the transplant patients to detect rejection.

Catheterization procedure and study protocol. Medical therapy was continued in all patients (Table 1). After intravenous administration of 10,000 IU heparin and 250 mg acetylsalicylic acid, right heart catheterization was performed with a 7F balloon-tipped flow-directed thermodilution catheter. A 7F temporary pacemaker was positioned into the right atrium. Left heart catheterization was carried out with a double-sensor high-fidelity pressure sensor pigtail catheter (Sentron, Roden, the Netherlands) for simultaneous recordings of LV and aortic pressures. The following parameters were evaluated: mean central venous pressure, mean pulmonary wedge pressure, LV systolic and end-diastolic pressure, and aortic pressures. After acquisition of these data, LV angiography and coronary angiography were performed with standard techniques (1,11). A Doppler guide wire with a floppy distal end (Cardiometrics, Inc., Mountain View, California) was introduced through an 8F guiding catheter and positioned at the midsegment of the left anterior descending coronary artery (LAD) and circumflex coronary artery (LCx), respectively, to measure Doppler flow velocity at rest and after hyperemia.

Table 1. Demographic, Echocardiographic, and Angiocardigraphic Characteristics of the Patient Population and Control Group

	HCM	Control
Age (yrs)	45.5 ± 14.6	48.7 ± 6.0
Symptoms		
Angina	5	0
Dyspnea	9	0
Syncope	2	0
Therapies		
Beta-blockers	5	0
Ca ²⁺ -antagonists	5	8
Immunosuppression	0	8
Aspirin	0	5
Dipyridimole	0	4
Echocardiography		
IVS-W _{th,ed}	26 ± 3	11 ± 3*
PW-W _{th,ed}	14 ± 1	11 ± 1
IVS-W _{th,%}	14 ± 1	37 ± 3*
PW-W _{th,%}	29 ± 2	38 ± 1*
Angiography		
QCA _{lad}	3.0 ± 0.8	3.0 ± 0.5
QCA _{lcx}	3.3 ± 0.8	3.1 ± 0.4

*p < 0.05 control versus HCM.

HCM = hypertrophic cardiomyopathy; IVS = interventricular septum; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LVSP = left ventricular systolic pressure; PW = posterior wall; QCA = quantitative coronary angiography; W_{th,ed} = wall thickness at end diastolic; W_{th,%} = percentage wall thickening.

Hearts of patients with HCM and HTX were paced at a constant heart rate of 100 beats/min to keep myocardial metabolism constant and avoid metabolic vascular adaptations of the coronary bed during the determination of the CFR. After optimization of the settings of the velocity signal and 3 to 5 min after intracoronary injection of a bolus of 2 to 3 mg isosorbide dinitrate, baseline recordings of flow velocity and perfusion pressure were collected and digitized at a sample rate of 125 Hz, for off-line analysis. Maximal velocity was induced by an intracoronary bolus injection of 18 μg adenosine. This dose of adenosine has been shown to produce maximal vasodilation in humans (11,12). The measurements of coronary flow velocity, before and after adenosine, were repeated after appropriate positioning of the Doppler wire in the LCx.

In a subset of patients with HCM (n = 9), esmolol (500 μg/kg/min) was infused to evaluate the effect of alterations in extravascular compression on the coronary microcirculation. To avoid concomitant changes in vasomotor tone, maximal vasodilation was induced by an adenosine infusion, which was started during the infusion of esmolol.

Doppler-derived conductance measurements. The sample volume from the Doppler wire is positioned at a distance of 5.2 mm from the transducer and has an approximated width of 2.25 mm. A power spectral analysis based on a Fast Fourier Transform algorithm is used, and the maximal Doppler shift is tracked and converted to the instantaneous velocity values (cm/s) (11,12). This signal and the LV pressure, the electrocardiogram, and aortic pressure are digitized at a sample rate of 125 Hz with a commercially

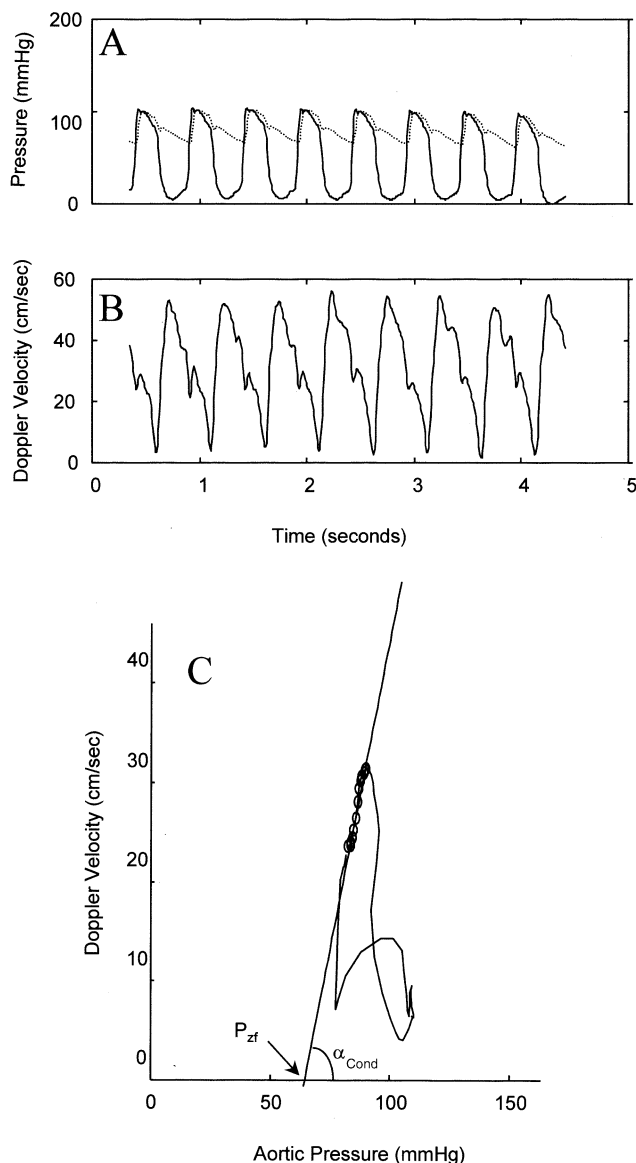


Figure 1. Representative recording of the aortic and left ventricular pressure (A) and Doppler signals (B) and the construction of the pressure-velocity loop (C). Indicated in the pressure velocity loop are the calculation of conductance (α_{cond}) and the zero pressure velocity intercept (P_{zf}).

available Analog-Digital Converting system (Acodas, DataQ Instruments, Akron, Ohio). The signals are analyzed off-line with an in-house developed software package (Mathworks Inc., Natick, Massachusetts). Briefly, start and end of a series of heartbeats are selected manually, followed by an automatic selection of individual heartbeats on the basis of the derivative of LV pressure. The diastolic pressure and velocity points are identified on the basis of the maximal velocity (start diastole) and the rise of the diastolic LV pressure (end diastole), and pooled for each series of heartbeats. Linear regression is then applied to obtain the slope (coronary conductance) (Fig. 1) and zero-pressure velocity intercept (P_{zf}) (Fig. 1) of the regression line.

Quantitative angiographic measurements. The guiding catheter, filmed devoid of contrast medium, was used as a

scaling device. A previously validated on-line analysis system operating on digital images (ACA-DCI, Philips, Eindhoven, the Netherlands) was used to calculate the end-diastolic and end-systolic diameter of the LAD and LCx and the proximal part of the first septal branch. Care was taken to select the portion of the segments in the LAD and LCx where the sample volume of the Doppler wire was located. The vessel diameters were used to calculate the vessel lumen area assuming a circular shape of the vessel. This vessel area was multiplied with the spatially averaged Doppler velocity (assuming a parabolic profile) to obtain coronary flow measurements in ml/min.

Echocardiographic measurements. Two-dimensional echocardiographic studies were performed with a commercially available echocardiography machine (HP Sonos 5500, Andover, Massachusetts). The heart was visualized from standard cross-sectional planes, and images were recorded on videotape (VHS) for off-line analysis. Septal and posterior LV wall thicknesses were measured in diastole from both the parasternal short-axis and long-axis views. From the recordings on videotape, representative frames from the various cross-sectional planes were acquired to determine septal and posterior LV wall thickness with the aid of a dedicated software program. All data from the various cross-sectional planes for the septal and posterior wall thickness were pooled per location.

Histological measurements. The myocardial material for the HCM group ($n = 11$) and the HTX group ($n = 9$) was fixated with paraformaldehyde and immersed in 10% buffered formalin. A von Giesson staining was used for identification and analysis of intramyocardial small arteries. Occurrence of dysplastic intramyocardial small arteries in each segment was scored semiquantitatively according to the following scale: 1: 0% to 10%, 2: 10% to 25%, 3: 25% to 50%, and 4: >50%. The degree of fibrosis was also evaluated with the elastic von Giesson staining. A semiquantitative approach was used, according to Maron (16), with the following scale: 1: 0% to 10%, 2: 10% to 25%, 3: 25% to 50%, and 4: >50%.

Analysis and statistics. The ratio of hyperemic over baseline conductance was calculated and referred to as diastolic coronary vascular conductance reserve (DCVR). Coronary flow reserve was calculated as the ratio of basal over hyperemic time-averaged velocity. Similar heartbeats were analyzed for the calculation of both indexes. We generated a receiving operator curve (ROC) for the classical CFR, the new DCVR, and the basal conductances with the data from the control group and from the LAD and LCx regions of the HCM group applying standard methods (19). The area under the ROC (area under the curve [AUC]) is often used as a reliable statistical parameter to evaluate the quality of a new diagnostic parameter. In addition, the variation in the conductance, the conductance ratio, the zero-flow pressure intercept, the Doppler velocity, and the CFR were quantified with the coefficient of variation.

All data are presented as mean \pm SEM. To evaluate the

Table 2. Hemodynamic Characteristics of the Patient Population and Control Group

	Control		
	Rest	Adenosine	Esmolol + Adenosine
LVSP	121 ± 5	119 ± 5	
LVEDP	11.6 ± 1.9	5.4 ± 1.4*	
AOP	120 ± 5	119 ± 5	
AV gradient	3 ± 3	4 ± 2	
	HCM		
	Rest	Adenosine	Esmolol + Adenosine
LVSP	167 ± 21	177 ± 9	154 ± 14
LVEDP	22.3 ± 2.2	15.7 ± 2.3*	9.5 ± 1.9*†
AOP	103 ± 5	105 ± 4	98 ± 5
AV gradient	75 ± 15	75 ± 13	55 ± 12†

*p < 0.05 vs. rest; †p < 0.05 vs. adenosine.

AOP = aortic pressure (mm Hg); AV gradient = gradient over the aortic valves (mm Hg); HCM = hypertrophic cardiomyopathy; LVEDP = left ventricular end-diastolic pressure (mm Hg); LVSP = left ventricular systolic pressure (mm Hg).

differences between the LCx and LAD regions of the HCM and the control group, an analysis of variance was used applying a standard software package (SPSS, Chicago, Illinois), followed by a modified Student-Newman-Keuls test for significant differences. The contribution of the hypertrophic process to the decrements of the DCVR was evaluated according to a linear regression model. All statistical tests were set at p < 0.05.

RESULTS

Patient characteristics. The HTX group, who served as controls, had no cardiac complaints, and all of them had a normal coronary angiogram. The age distribution between HCM and control groups was similar (Table 1). However, despite medical therapy with beta-blockers and/or calcium antagonists, most of the HCM patients were symptomatic (New York Heart Association II or III), while the recipients were symptom free. Furthermore, the HTX group showed no sign of rejection as based on objective analysis of biopsies. By quantitative coronary angiography (QCA), coronary vascular diameters were similar in both groups.

Systemic hemodynamic. Left ventricular systolic pressure and end-diastolic pressure were significantly larger in patients with HCM as compared with controls. In addition, a LV outflow tract pressure gradient was present only in patients with HCM (Table 2). Adenosine reduced end-diastolic pressure in both groups. Esmolol reduced end-diastolic pressure (from 15.7 to 9.5 mm Hg) and the AV gradient (from 75 to 55 mm Hg).

QCA. Diastolic and systolic diameters of the LAD were 1.3 ± 0.3 cm and 1.4 ± 0.3 cm, respectively. Adenosine increased diameters to 3.0 ± 0.8 cm and 3.3 ± 1.0 cm for diastole and systole, respectively (p < 0.05 vs. control). Additional esmolol did not affect the diameter in diastole (3.0 ± 0.5 cm) or in systole (3.1 ± 0.4 cm).

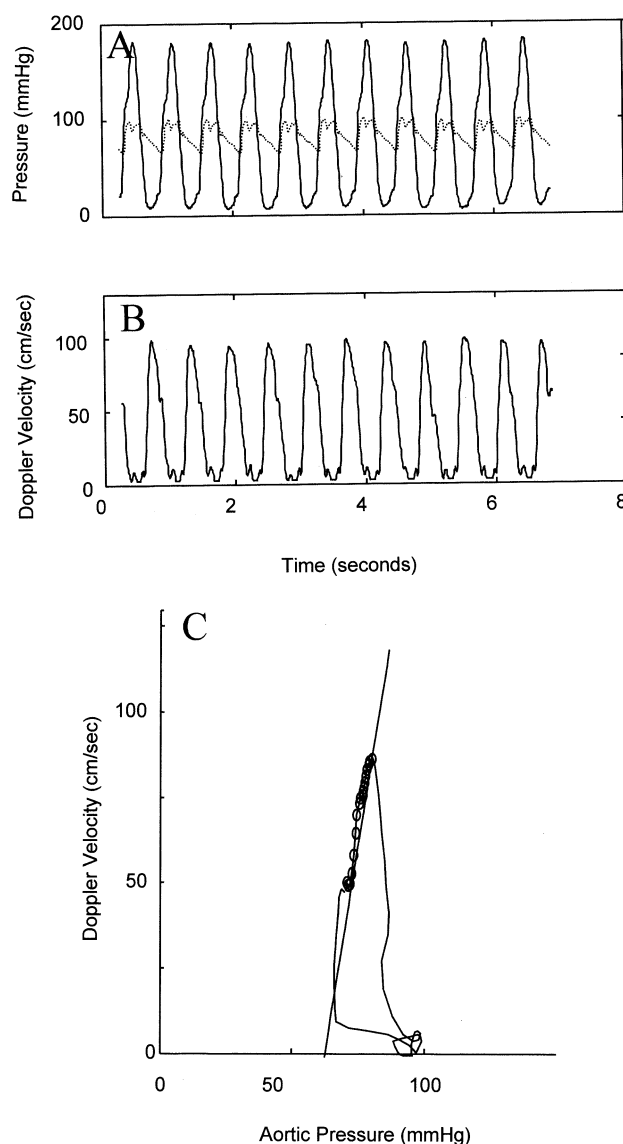


Figure 2. Aortic pressure, left ventricular pressure (A), and Doppler velocity (B) recordings from a typical hypertrophic cardiomyopathy patient plus the reconstruction of aortic pressure-Doppler velocity loops according to Mancini *et al.* (C).

CFR and diastolic conductance. At least 10 consecutive beats were analyzed for the calculation of each variable (Figs. 1 and 2). Coronary conductance during resting conditions increased progressively from a low level in the control group (0.8 ± 0.1 mm Hg/s/cm) to a high value in the septal region of the HCM group (1.8 ± 0.2 mm Hg/s/cm) with the LCx region in between both regions (1.2 ± 0.3 mm Hg/s/cm) (Table 3, Fig. 3). Maximal coronary conductances were similar for the LCx and LAD region in the hypertrophic cardiomyopathy, and the LAD regions of the control group (Fig. 3), resulting in a DCVR pattern that resembled the minimal conductance (Table 3, Fig. 3). Coefficient of variation for the conductance during baseline and hyperemia were $9 \pm 9\%$ and $9 \pm 8\%$, respectively. The coefficient of variation for the DCVR was $15 \pm 12\%$.

Table 3. Coronary Flow and the Slope of the Pressure-Flow Loops Measured in the LAD and LCX of the HCM Group (n = 11) and the LAD of the Control Group (n = 9)

	HCM-LAD	HCM-LCX	Control
Coronary flow (cm/s)			
Basal velocity	34.1 ± 7.0	33.4 ± 8.3	20.2 ± 3.5
Hyperemic velocity	53.5 ± 12.1	59.0 ± 12.7	49.3 ± 6.9
CFR	1.5 ± 0.2	1.7 ± 0.2	2.5 ± 0.3*‡
Coronary conductance (mm Hg/s/cm)			
Basal conductance	1.8 ± 0.2	1.2 ± 0.3†	0.8 ± 0.1*
Hyperemic conductance	2.5 ± 0.3	3.0 ± 0.3	2.6 ± 0.4
DCVR	1.5 ± 0.2	2.9 ± 0.4†	3.3 ± 0.5*‡
Zero-flow pressure intercept (mm Hg)			
Basal conductance	49.9 ± 13.2	41.8 ± 17.4	39.2 ± 22.7
Hyperemic conductance	47.1 ± 19.6	41.9 ± 18.8	26.7 ± 15.3

*p < 0.05 HCM-LAD vs. control †p < 0.05 LAD vs. LCX in HCM group ‡HCM-LCX vs. control.

Control = donor heart recipients; DCVR = diastolic coronary vasodilator reserve; HCM = hypertrophic cardiomyopathy; LAD = left anterior descending artery; LCX = left circumflex coronary artery; mm Hg/s/cm = millimeter mercury times seconds per centimeter.

Zero-velocity pressure intercepts (P_{zf}) were similar for HCM and control during resting conditions and hyperemic conditions (Table 3). Coefficient of variation of the P_{zf} were

25 ± 24% and 35 ± 33% for baseline and hyperemic conditions.

Doppler-derived diastolic velocities during baseline were 31.8 ± 4.7 cm/s, 37.3 ± 6.6 cm/s, and 34.4 ± 9.0 cm/s for the LCx, LAD, and control, respectively. During hyperemia, these values were 56.7 ± 10.3 cm/s, 56.4 ± 9.1 cm/s, and 80.3 ± 12.1 cm/s. All values were nonsignificant different between groups and increased after hyperemia. Doppler-derived systolic velocities during baseline were 3.3 ± 1.2 cm/s, 2.1 ± 1.1 cm/s, and 9.2 ± 2.6 cm/s for the LCx, LAD, and control vessels, respectively, while these values during hyperemia were 6.4 ± 2.4 cm/s, 7.9 ± 3.5 cm/s, and 27.5 ± 5.0 cm/s. In both conditions, the systolic velocity in the control vessel was larger than the systolic velocities in the HCM-LCx and HCM-LAD vessels. Ratio of diastolic hyperemic velocities over diastolic baseline velocity was 2.3 ± 0.8, 1.6 ± 0.2, and 2.7 ± 0.3, for the LCx, LAD, and control group, respectively. These values were not significantly different.

The time-averaged coronary flow velocities during resting conditions tended to be higher in HCM than in control patients (Table 3). After hyperemia, coronary flow velocity was similar for HCM-LAD, HCM-LCx, and control

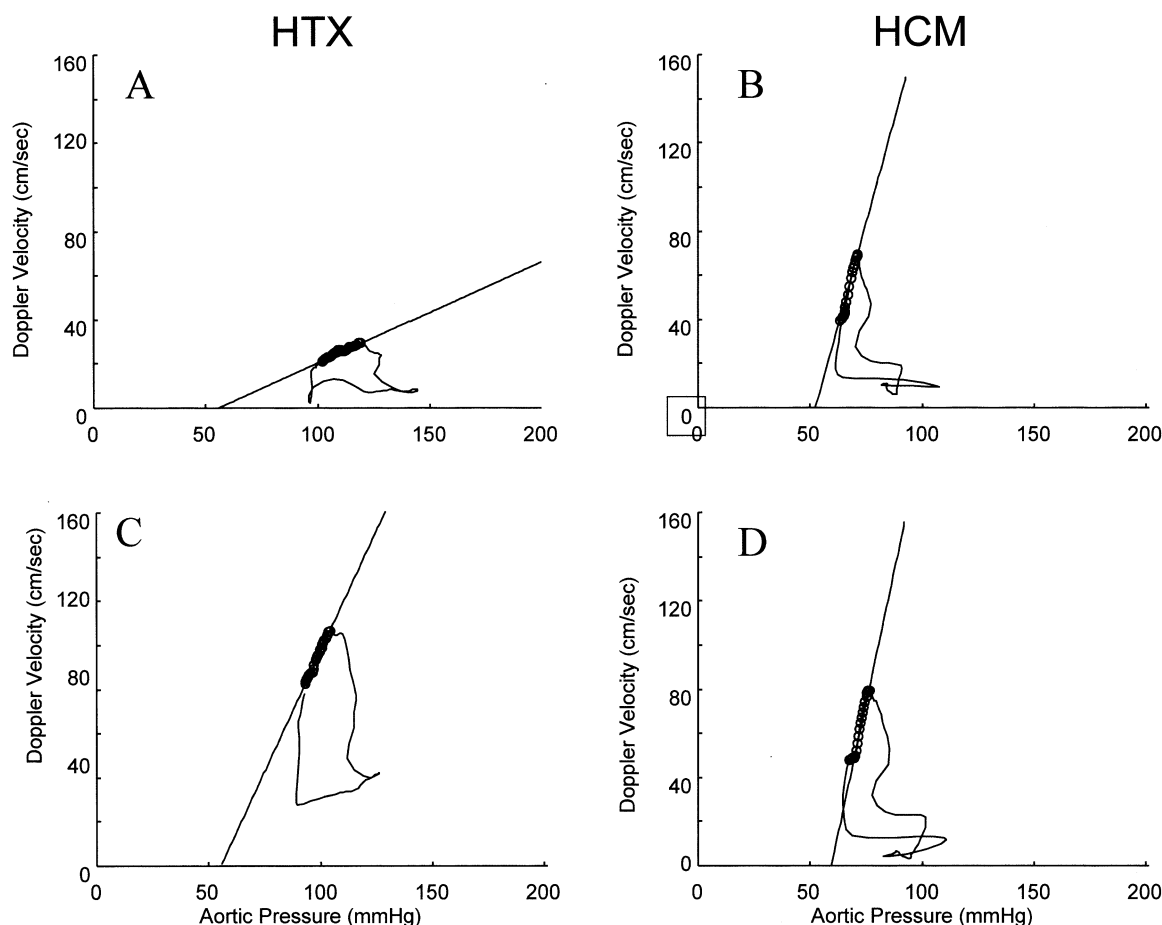


Figure 3. Representative recordings of the pressure-coronary velocity loops in the heart transplant recipients (HTX) (A, C) and hypertrophic cardiomyopathy patients (HCM) (B, D) during resting conditions (A, B) and after maximal hyperemia (C, D).

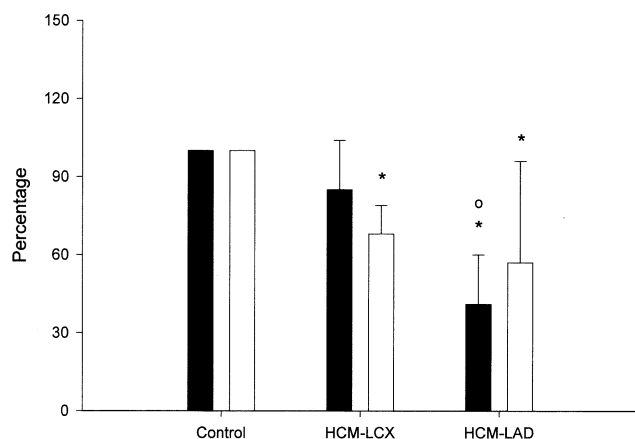


Figure 4. Relative changes in both the coronary flow reserve (solid bars) and the diastolic conductance reserve (open bars). * $p < 0.05$ vs. control; ° $p < 0.05$ vs. hypertrophic cardiomyopathy-left circumflex coronary artery (HCM-LCx). LAD = left anterior descending coronary artery.

(Table 3). The CFR was decreased in the HCM group both in the LAD and LCx regions, which was slightly more pronounced in the LAD region (Table 3). The coefficient of variation of the Doppler-derived velocities were $6 \pm 6\%$, $5 \pm 5\%$, and $11 \pm 10\%$ for baseline, hyperemia velocities, and CFR, respectively.

The CFR in the HCM-LAD and the HCM-LCx region decreased to $57 \pm 7\%$ and $64 \pm 7\%$ of control, while the CFR in the HCM-LCx and HCM-LAD regions were similar. In contrast with the CFR data, the DCVR for the LCx region was $86 \pm 12\%$ ($p > 0.05$ vs. control) of the control group, while the DCVR in the HCM-LAD region was $46 \pm 3\%$ of the control group ($p < 0.05$ vs. control) (Fig. 4). Now the HCM-LAD and HCM-LCx DCVRs were different (Fig. 4). The ROC analysis revealed that the AUC for the CFR data tended to be smaller (0.76) than for the DCVR data (0.85, $p > 0.05$). In addition, a ROC analysis performed on basal conductances alone produced an AUC similar to the DCVR (0.86). Part of the variability of the CFR and DCVR could be explained by the hypertrophic process itself, as both parameters were related to wall thickness according to the following equations: $\text{CFR} = -0.05 \text{ Wth} + 3.02$ ($r^2 = 0.2$, $p < 0.05$) and $\text{DCVR} = -0.12 \text{ Wth} + 4.4$ ($r^2 = 0.7$, $p < 0.05$, Fig. 5).

During esmolol, the hyperemic coronary conductance did not change (3.1 ± 0.5 and 3.1 ± 0.9 mm Hg/cm/s, $n = 9$). Furthermore, P_{zf} also remained unchanged (57 ± 15 mm Hg vs. 53 ± 7 mm Hg, $n = 9$), indicating that changes in systolic compression have minor effects on diastolic coronary conductance.

Echocardiography. End-diastolic septal wall thickness was significantly increased in HCM as compared with HTX (Table 1, $p < 0.05$). Percent wall thickening, an index for regional contractile function, of the interventricular septum was decreased (Table 2). Similar changes were noted for the posterior wall; wall thickness was increased by 30%, and percent wall thickening was significantly decreased ($p <$

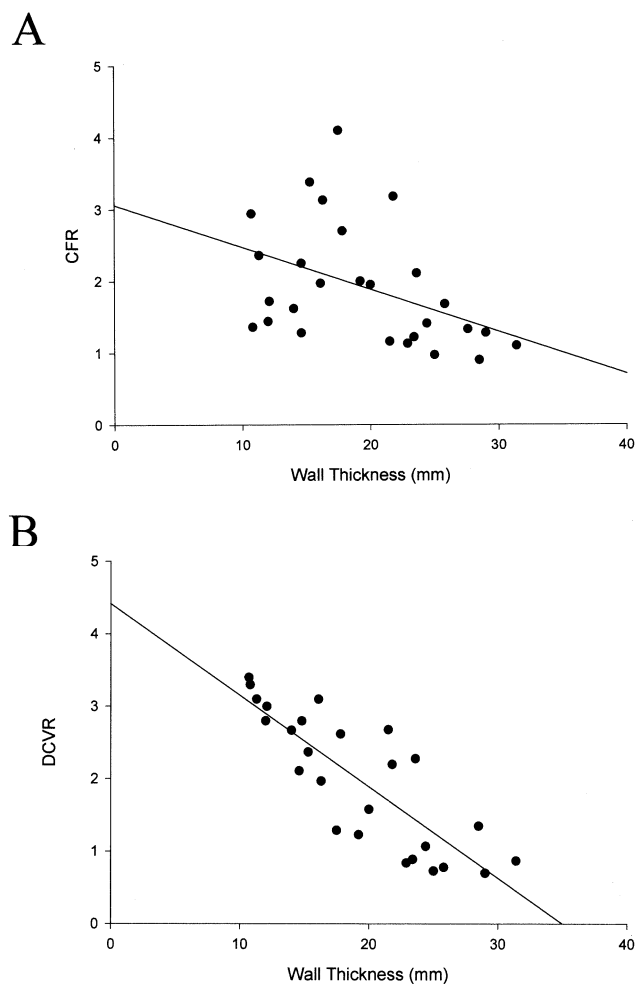


Figure 5. Relation between wall thickness and coronary flow reserve (A) and diastolic coronary vascular conductance reserve (B) for all three vessel territories combined.

0.05). Esmolol reduced wall thickening of the posterior wall from $26 \pm 4\%$ to $15 \pm 4\%$ ($p < 0.05$), and of the septal wall from $7 \pm 3\%$ to $4 \pm 1\%$ ($p = 0.06$).

Histological analysis. ARTERIOLAR DYSPLASIA. In the control group, only two specimens scored group II and IV, resulting in an average score of 1.1. In HCM, however, this score was 2.2 (range: 1.8 to 4.8, $p < 0.05$).

FIBROSIS. All individuals of the control group scored category I ($<10\%$ fibrosis), while the HC group scored 2.2 (range: 1 to 4; $p < 0.05$).

DISCUSSION

Ventricular hypertrophy is associated with disturbances in the microcirculation leading to a decreased perfusion. In addition, in a subset of patients with HCM, extravascular compression may be increased due to the high LV pressure or to changes in contractility accompanying this disorder. To identify changes in the microcirculation apart from changes in systole, a diastolic flow index might be of value. In the present study, it could be shown that: 1) the diastolic

conductance, during maximal hyperemia, was independent of the preceding systolic compression; 2) a ratio of diastolic conductances was sensitive in detecting perfusion abnormalities in the septal bed of HCM patients, where disturbances in the microcirculation were measured; 3) diastolic velocity ratio followed a similar pattern, but due larger variability is less suited to detect differences; and 4) no changes were found in the LCx region of HCM patients, while the classical CFR detected abnormalities. The latter finding is probably due to the accompanying systolic extravascular compression, and might explain why the DCVR was better correlated with changes in the degree of hypertrophy than the classical CFR. In addition, the changes in the DCVR are (partly) explained by changes in the basal conductances. This observation explains similarity in ROC analysis of the DCVR and basal conductances.

Hypertrophy is also accompanied by decrements in CFR (13-15). Convincing evidence has been presented relating changes in the coronary microcirculation to decrements in CFR (13-16). It is also known that extravascular compression of the microcirculation is increased in hypertrophy (13-16). As both processes are present in HCM patients (16,17), it is of importance to develop an index sensitive for one of these mechanisms. Coronary flow reserve is based on time-averaged values and is, therefore, affected both by extravascular compression and by changes in the coronary microcirculation.

We propose that the DCVR is less sensitive to extravascular compression than the classical CFR, as esmolol did not affect hyperemic conductance. Esmolol did affect, however, local wall thickening and LV systolic pressure, which implies that, at constant heart rate, it affected myocardial contractility. Contractility and systolic LV pressure are the most important components of extravascular compression. Concomitant hyperemia was induced to avoid vasomotor changes induced by the accompanying reduction in oxygen consumption induced by the reduction in pressure and contractility. A ratio of diastolic velocities, not including pressure measurements, displayed a similar pattern as the DCVR signifying the diastolic behavior of the DCVR. However, the changes in this index did not reach statistical significance. This lack of significance may be due to the high sensitivity of diastolic velocity to changes in aortic pressure. The diastolic properties of the DCVR may explain the discrepancy of the CFR and the DCVR in the LCx region. The DCVR, however, is only decreased in the LAD-perfused region that displayed disturbances in the coronary microcirculation.

Increments in basal conductance with muscle mass reflect the increased oxygen demand of the increased muscle mass, while the absence of an increased hyperemic conductance may be explained by a lack of growth of the coronary microcirculation. A lack of growth of the microcirculation in hypertrophy has been described in the literature.

A large zero-flow pressure intercept was measured, which is due to a combination of large linear extrapolation and increased extravascular compression (3). The hyperemic

stenosis resistance index advocates also pressure and velocity measurements to characterize stenosis resistance (20). While the application is different, the argument to measure both pressure and flow to detect changes in resistance is similar. Application of this technique to a large patient group clearly showed improvement in diagnostic possibilities (20,21). The present study, with a much smaller number of patients, showed a trend towards similar findings. Further studies are necessary to prove similar results.

Methodological considerations. The beta-blockers used by the patients probably did not affect the global conclusions of the present study, as the hearts were paced, thereby correcting for the negative chronotropic effect of beta-blockers. Furthermore, as beta-blockers reduce myocardial oxygen demand, they tend to reduce basal flow velocity and coronary conductance, thereby increasing CFR in HCM. In addition, dipyridamole was given in the control group only (four patients), which could affect the outcome of the present study. However, a subanalysis excluding these patients showed that maximal velocity and maximal conductance was similar as compared with the entire control group, making this interpretation less likely.

Adenosine was given in combination with esmolol to avoid vasomotor changes induced by the concomitant reduction in myocardial oxygen consumption. Any difference in velocity during adenosine with esmolol is, thereby, the result of changes in extravascular compression (22).

The effects of HOCM, adenosine, and esmolol on QCA-derived diameters (Coronary Angiographic Acquisition System [CAAS II]) were larger than its reproducibility (0.09 mm) and accuracy (0.00 mm), as previously reported (23-26). Both the CFR and the DCVR are not normalized to changes in the size of the vascular bed. Therefore, changes with respect to the different beds may be masked. To estimate these changes, CFR and DCVR were both divided by wall thickness. This normalization did not change the overall conclusions.

Although both baseline and hyperemic measurements were performed in a single patient, the DCVR and CFR indexes reported reduce these repeated measures into a single number. Consequently, we applied a nonrepeated analysis of variance as a statistical test.

In conclusion, the ratio of hyperemic over resting conductance (DCVR) can be measured with high accuracy in patients with HCM and detects differences in HCM patients with respect to control. As the DCVR was not sensitive to systolic extravascular compression, and was associated with disturbances of the coronary microcirculation, it may be a new tool for studying changes in the coronary microcirculation in human disease states where LV hypertrophy is present.

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